**Exhibit A**

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Authentication of copy of documents concerning the Patent application for INDUSTRIAL INVENTION No. MI2002 A 002748

It is hereby certified that the attached copy is the true copy of the original documents filed with the above mentioned patent application whose data are shown in the enclosed filing certificate.

Rome, date

THE DIRECTOR
OF THE DIVISION

(signature)

SEAL

FORM A DUTY STAMP

TO THE MINISTRY OF INDUSTRY COMMERCE AND HANDICRAFT
Main Patent Office - ROME
Patent Application for Industrial Invention, filing of reserves, advanced opening to public inspection

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D. TITLE proposed class, (sec./cl./ucl.) A61K group/subgroup 9

Stabilised solid drug dispersions in an organic carrier and a procedure for preparing the same

ADVANCED OPENING TO PUBLIC INSPECTION yes___ no_x__
in presence of amendment request: date no. of ref.:

E. NAMED INVENTORS

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| 1) COLOMBO Italo | 3) |
| 2) GERVASONI Dario | 4) |

F. PRIORITY
Country or Exhibition Type of Priority Appln. No. Appln. date Encl(yes/res)

1) NONE

2)

G. CENTRE FOR COLLECTING MICROORGANISMS'CULTURES, denomination

H. SPECIAL NOTES
None

ENCLOSED DOCUMENTS

Specimen No. RESERVES
DISSOLUTION
Doc. 1) 2 prov. no. sheets 26 abstract with main drawing, spec. and claims (compulsory 1 copy) date No. of ref.
Doc. 2) 2 prov. no. sheets 03 drawing (compulsory if cited in description, 1 copy)
Doc. 3) 1 res. power of attorney or reference attorney
Doc. 4) 0 res. designation of inventor
Doc. 5) 0 res. priority document with Italian translation comparison single priority
Doc. 6) 0 res. authorisation or assignment deed
Doc. 7) 0 res. complete name of the applicant

8) PAYMENT RECEIPT OF EURO TWOHUNDREDNINETY/80 compulsory
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The applicant's signature for EURAND INTERNATIONAL S.p.A.
Dr. Diego Pallini (signature)

follows yes/no NO
We required certified copy of the present deed yes/no YES

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CHAMBER OF COMMERCE INDUSTRY HANDICRAFT AND AGRICOLTURE OF MILAN code 15
FILING CERTIFICATE Application no. MI2002A 002748 Reg. A
The year 2002 the 23rd day of the month of December

The above mentioned applicant(s) has(have) presented to me undersigned the present application consisting of no. 00 additional sheets for the grant of the above patent.

I. DIFFERENT NOTES OF THE RECORDING OFFICER
none

THE DEPOSITER
(signature)

THE RECORDING OFFICER
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SEAL

FORM A

ABSTRACT OF THE INVENTION TOGETHER WITH MAIN DRAWING, SPECIFICATIONS AND CLAIMS

Application No. MI2002A 002748 Filing date 23/12/2002
Patent No. Date of grant

D. TITLE

Stabilised solid drug dispersions in an organic carrier and a procedure for preparing the same

L. ABSTRACT

New solid drug dispersions are described in which the drug is present in amorphous form and massively dispersed (in bulk) inside the particles of an organic carrier. These dispersions are obtainable by mixing together the drug and the organic carrier under particular experimental conditions, and applying an oscillating electromagnetic field to the mixture, to a frequency belonging to the microwave region.

With respect to the known techniques, the present invention allows to increase in the amount of drug incorporated into the carrier in amorphous form, and to increase the physical stability of the amorphous phase. This is particularly useful in the preparation of pharmaceutical compositions based on drugs which are crystalline in nature, such as are notoriously sparingly soluble in water: thanks to the increased amounts and stability of the drug in amorphous form, the resulting formulations have a more rapid and intense effect, and are endowed with greater bioavailability.

M. DRAWING

Description of the invention for industrial invention having for title:

Stabilised solid drug dispersions in an organic carrier and a procedure for preparing the same

in the name of EURAND INTERNATIONAL S.p.A.

residing in MILANO MI 2002A 002748

named inventors: COLOMBO Italo, GERVASONI Dario

* * * * *

SEAL

**FIELD OF THE INVENTION**

The present invention refers to the field of rapid effect pharmaceutical compositions provided with high bioavailability. The preparation of new drug-carrier composites (stabilised solid dispersions) is described in which the drug is massively dispersed (in bulk) in amorphous form inside an organic carrier.

**PRIOR ART**

The attainment of ready to use pharmaceutical compositions, which ensure high solubilisation kinetics of the active ingredient and therefore a high bioavailability immediately following administration, is an important objective in pharmaceutical technology; such a need is particularly felt in the case of active ingredients sparingly soluble in water, which notoriously have a low bioavailability.

Many active ingredients poorly soluble in water are present in the crystalline state: a system to improve the solubility of this group of drugs is that of destructuring the crystalline network, rendering them amorphous: in fact a substance in the amorphous state has both greater solubility and faster dissolution kinetics in water with respect to the corresponding crystalline state. The reason for which lies in the fact that whilst the dissolution of a crystal requires an additional intervention on the part of the solvent to break the intermolecular bonds in the crystalline network, such an intervention is not required in the case of the amorphous form: in the latter case the dissolution procedure requires less energy and the dissolution takes place more rapidly.

The amorphisation procedures for crystalline drugs have been known for a long time (*Yu L., Amorphous pharmaceutical solids: preparation characterization and stabilization. Adv. Drug. Delivery Rev.*, 2001, 48, p. 27-42.). However, due to the greater stability of crystals, (a physical form with lower free energy and, therefore, thermodynamically more stable) the amorphised drugs have poor stability (metastable phase) and tend to easily recrystallise, thus losing their temporarily acquired increased solubility.

With the aim of limiting this phenomenon, it has been proposed to make the amorphous active ingredient deposit on the pharmaceutical carriers: in this case, the drug-carrier interactive forces limit the tendency of the amorphous phase molecule to re-aggregate, which allows them to have a greater stability. To obtain that, "solvent deposition" procedures have been proposed, according to which the active ingredients are initially dissolved in an appropriate solvent; to this solution are

added insoluble carrier particles, and then the solvent is evaporated, thus making the drug in amorphous form precipitate on the carrier.

These solutions however are only partially effective, in that they lead to not very high percentages of amorphisation; in addition, the drug remains deposited only on the external surface of the carrier particles, i.e. not distributed internally (in bulk) inside the particles themselves (*International Journal of Pharmaceutics*, 33, 1986, p. 115-124): the drug lying on the surface still shows a notable freedom for re-aggregation easily forming crystalline structures. Recently, some authors (*Drug Dev. Ind. Pharm.*, 24(4), 1998, p.359-363) have proposed the use of microwaves to increase the solubility of crystalline drugs: the procedure provides the mixing of drug with an inorganic carrier with a high surface area (silicon dioxide), and exposure to microwaves; however, even in this case composites are obtained, denominated by the authors "*surface solid dispersions*", in which the amorphised drug is localised on the surface of the carrier particles. Even in this case the limitations of the previous systems are present, i.e. the drug is deposited only on the external surfaces of the carrier particles, and is therefore still subject to the phenomenon of re-crystallisation.

Synthetically, all the above systems do not allow the attainment of high quantities of amorphised drug and at the same time high stabilisation of the same. The present invention effectively answers such a need.

**SUMMARY**

It has now been surprisingly found that when an active ingredient is mixed with an organic carrier and then treated with an oscillating electromagnetic field at frequencies belonging to the microwave region, a drug-carrier composite is obtained in which the drug is amorphised in higher quantities and in more stable form, with respect to these obtained by the prior art.

In the present invention the treatment with microwaves is carried out on homogeneous mixtures of drug and carrier pre-wetted with appropriate quantities of solvents, or on drug-carrier mixtures in the dry state, placed on dielectric material based supports which couple with the microwaves, such as for example polytetrafluoroethylene loaded with graphite.

In particular, the composites obtained according to the present invention, herein identified as "stabilised solid dispersions", are characterised by containing a quantity of amorphised drug greater than 50 % by weight with respect to the total active ingredient present, and by the fact that the drug is also dispersed inside (in-bulk) of the carrier particles, hence not just on the external surface of the same.

The present dispersion technique in-bulk of the active ingredient in amorphous form is seen as being particularly effective and useful in the case of drugs poorly soluble in water, thus allowing the increase in the characteristics of solubility and bioavailability in rapid times following administration.

**DESCRIPTION OF THE DRAWINGS**

Figure 1: calibration lines for the Ibuprofen β-cyclodextrine, Ibuprofen Crosspovidone and Nifedipine Crosspovidone systems.

● : Ibuprofen / beta-Cyclodextrine

■ : Ibuprofen / Crosspovidone

▲ : Nifedipine / Crosspovidone

Figure 2: strength (------) and temperature (———) profiles obtained during the treatment of the sample PVP/Nif01.

Figure 3: strength (------) and temperature (———) profiles obtained during the treatment of the sample PVP/Nim06.

**DETAILED DESCRIPTION OF THE INVENTION**

A first subject of the invention is constituted by new composites containing an active ingredient dispersed in an organic carrier, in which the active ingredient is:

- present in amorphous form in quantities greater than or equal to 50 % by weight with respect to the total of the active ingredient present in the composite, and
- massively dispersed ("in-bulk") within the particles of the above mentioned carrier.

By "active ingredient in amorphous form" is intended the active ingredient when present in the form of molecular clusters, the structural organisation of which is not discernable with X-ray diffraction techniques (PXRD) or by differential scanning calorimetry (DSC). Preferred composites are these which contain at least 75%, or more preferably at least 85% of the drug in amorphous form; composites in which the drug is present at 100% in amorphous form have been obtained with the present invention, and are described in the experimental section.

For "massively dispersed (or in-bulk)" is intended the fact that the drug is deposited not only on the surfaces of the carrier particles, but also inside them: in the present invention the drug is made to diffuse inside carrier particles and stabilised "in situ".

The organic carrier is preferably selected from an insoluble cross-linked polymer, a hydrosoluble complexing agent or mixtures thereof. The term "insoluble" is referred with respect to water as a solvent, at room temperature (20°C); the term "cross-linked" refers to the existence of natural or synthetically induced inter-polymer bonds; a preferred example of an insoluble cross-linked polymer is cross-linked polyvinylpyrrolidone, commercially known as crosspovidone; other examples of polymers of this class are cross-linked sodium-carboxymethylcellulose, cross-linked starch, cross-linked dextran, cross-linked polystyrene, cross-linked beta-cyclodextrine.

Preferred composites of the class of hydrosoluble complexing agents are cyclodextrines (such as for example: alpha-, beta-, gamma-cyclodextrine and derivatives thereof), maltodextrine, microcrystalline cellulose. The hydrosoluble complexing agents can contain water molecules of hydration.

The organic carriers used in the present invention are characterised by non high surface area, for example, comprised of between 0.05 and 20 $m^2/g$; for example the CL-PVP and cyclodextrine commercially available meet these requirements perfectly, with an average surface area of 0.5-2 $m^2/g$.

The present invention also comprises the use of mixtures of two or more organic carriers: for example the mixture of an insoluble cross-linked polymer with a hydrosoluble complexing agent.

Any active ingredient of pharmaceutical interest (also including mixtures of two or more of them) can be present in the composites claimed by the present invention; active ingredients sparingly

soluble in water are preferred, also known as belonging to the class II of the biopharmaceutical system of classification (cf. *Guidance for Industry: Immediate Release Solid Oral Dosage Forms*, Ed. Centre for Drug Evaluation and Research, FDA, 1997): examples of such compounds are nimesulide, ibuprofen, nifedipine, grisofulvine, piroxicam, progesterone, indomethacine, lorazepam, etc. As shown in the experimental section, it has been possible to obtain high to complete amorphisation of these products (originally present in the crystalline state with low solubility) and their dispersion in-bulk within the carrier.

In the composites according to the invention, the active ingredient and the carrier are present in weight ratios preferably comprised of between 1:0.5 and 1:20, more preferably between 1:1 and 1:10.

The preparation procedure of the composites constitutes a second subject of the invention. The procedure comprises the mixing of the original drug (that is the drug in microcrystalline structure which it is intended to make amorphous and disperse within the carrier) with the above mentioned organic carrier, followed by treatment with an oscillating electromagnetic field, at a frequency belonging to the microwave region, with the following particulars:

(i) the application of the oscillating electromagnetic field is carried out on the previously wetted drug-carrier mixture, or

(ii) the application of the oscillating electromagnetic field is carried out on the drug-carrier mixture placed in a container constituted of a dielectric material having coupling capacity with microwaves.

In the first variant (i), the drug-carrier mixture is wetted with an appropriate amount of solvent, until forming a sufficiently dampened mass; the solvent, generally water, is added using known techniques, for example by nebulisation of the solvent through the mixture kept stirring, or simply pouring onto the mixture and mixing it. The solvent is added in an amount comprised of between 0.1 ml/g and 5 ml/g with respect to the dry drug and carrier mixture. The mixture, thus pre-wetted, placed in a conventional type reactor (for example a Pyrex glass container), is introduced into the oven and then treated with microwaves at pressure values equal to or greater than that of atmospheric, preferably comprised of between 1 and 20 bar.

In variant (ii), the drug-carrier mixture is placed in a sample holder (reactor) made entirely or partially (for example of at least 10%) of a dielectric material coupling with microwaves, and thus introduced into the microwave applicator. For "coupling capacity by microwaves" is intended the fact that the material in question, when exposed to microwaves, increases the temperature in proportion to the power applied; a preferred example of a material having this property is polytetrafluoroethylene loaded with graphite.

Using reactors containing the above mentioned coupling materials, the amorphisation proceeds easily at atmospheric pressure, without the need to operate at high pressure, and without the need to add water or other humectants; that does not preclude however the possibility of adding water and/or operating under pressure, whenever desired.

In both variants (i) and (ii), the application of the oscillating electromagnetic field is carried out with microwaves having energy comprised of between 100 W and 5000 W, for an overall time

comprised of between 5 and 120 minutes. The oscillating electromagnetic field can indifferently be focussed or non-focussed. The frequency range of the microwaves applied is generally comprised of between 400 MHz and 25000 MHz. The application of the microwaves can take place under conditions of constant or variable energy. In the first case a fixed energy value is imposed (for example 500W), which is maintained constant throughout the entire period of treatment. In the second case one can carry out a first step with a gradual increase in energy (for example for 10-25 min) until the sample reaches melting point; on reaching such a value, the energy administered is maintained constant (for example for 10-60 min).

At the end the treatment is suspended, allowing the sample to cool to room temperature, and the composite collected.

The equipment used for the application of the microwaves can be any microwave applicator which operates within the above described intervals and which (when desired) allows the modulation of the pressure to which the sample is exposed. Such applicators are known *per se* and already used in the pharmaceutical field for various applications, for example to evaporate solvents. They are generally made up of a microwave generator, a wave guide and an application chamber; the generator is a "magnetron" electronic tube; the wave guide is a corridor, the walls of which are metallic, through a multiple reflection mechanism, they transmit the wave towards the application chamber in which the material is exposed to the microwaves. The applicators are conveniently fitted with power distribution management and control systems, for the sample temperature and the pressure to which the sample is exposed. Specific examples of the distributors used in the present invention are the Prolabo "Synthewave 402" (monomode applicator for focussed microwaves, freq. 2.45 GHz, max. power. 300 W), or the Mileston "Microsynth" (multimode applicator non-focussed microwaves, with pre-mixing chamber and pyramidal diffuser, maximum power 1000 W).

With respect to what allowed by the known art surface amorphisation, amorphisation in-bulk obtained by the present invention allows great exploitation of the entire volume of the available carrier for the incorporation of the drug in amorphous form: it therefore becomes possible to incorporate into the carrier, significantly greater quantities of amorphous drug with respect to that previously possible. Analogously, with equal amorphous drug content, it is possible to reduce the amount of carrier, thus realising lower volume pharmaceutical formulations (e.g. smaller pills), with important advantages both for the saving of excipient, the economy of the process and packaging, and for the ease of administration and acceptability on the part of the patient.

The composites (stabilised solid dispersions) obtained according to the present invention can be used directly as pharmaceutical compositions and as such administered to patients, or can be added to with excipients and treated according to conventional pharmaceutical techniques with the aim of obtaining pharmaceutical forms suited to different administration needs. For example the composite can be integrated with disintegrants, glidants, lubricants, preservatives, sweeteners, other active ingredients, etc. The preparation procedures of pharmaceutical compositions are known *per se* and comprise for example granulation, compression, film-coating, encapsulation, micro-encapsulation, etc.; the pharmaceutical forms in which the composite can be formulated

include granulates for extemporaneous dissolution, pills, mini-pills, capsules, microcapsules, etc.

The present invention will now be described through the following example applications, which do not have limiting function.

EXPERIMENTAL SECTION

Materials and methods

1. Active ingredients

The materials subjected to treatment with microwaves are:

Ibuprofen, Nimesulide and Nifedipine, representatives of sparingly hydrosoluble drugs, belonging to the biopharmaceutical class II.

The thermal characteristics of Ibuprofen are the following:

Melting temperature $T_m$= 75.6 °C,

Melting enthalpy $\Delta H_m$= 126.6 J/g.

The thermal characteristics of Nimesulide are the following:

Melting temperature $T_m$= 148.9 °C

Melting enthalpy $\Delta H_m$= 111.1 J/g).

The thermal characteristics of Nifedipine are the following:

Melting temperature $T_m$= 172.7 °C

Melting enthalpy $\Delta H_m$= 101.4 J/g).

2. Organic carriers

- Crosspovidone, as an insoluble amphiphilic cross-linked polymer.
- β-cyclodextrine, as a carrier belonging to the class of the hydrosoluble complexing agents.

3. Microwave applicators

- The "Synthewave 402" monomode applicator from Prolabo, operating at a frequency of 2.45 GHz and with a maximum deliverable power of 300 Watts. With this type of applicator the field results as being focused in a restricted spatial volume containing the sample for treatment.
- The "Microsynth" multimode applicator from Milestone fitted with a premixing chamber with a pyramidal microwave diffuser to obtain optimal uniformity of the field. The applicator works with two continuous generation magnetrons (non pulsed) and distributes a maximum power of 1000 Watts.

Both applicators are equipped with control systems for the delivered power, the developed pressure (up to 20 bar) and the temperature of the sample. The control and monitoring system for the monitoring of the sample is constituted of two types of sensors: one fibre-optic and the other infrared (pyrometer).

4. Characterisation of the physical state of the drug in the composites

The degree of dispersion of the drug in the carrier has been evaluated by X-ray photo-electronic

spectroscopy (XPS or ESCA). This technique allows the quantitative measurement of the elementary composition of the surface layer of the material (thickness of the layer equal to 100-150 A) and therefore the possible excess or lack of drug molecules with respect to a homogeneous distribution. The percentage of crystalline residue has been calculated using the following relationship:

$$\%C = \frac{(\Delta H_a * 100)}{slope * T}$$

where %C is the residual percentage crystallinity of the drug, $\Delta H_a$ is the apparent specific enthalpy of fusion, determined by DSC, T is the percentage drug content in the system and the constant "*slope*" represents the angular coefficient of the calibration line obtained by measuring the enthalpy of fusion in drug-carrier physical mixtures pre-constituted with known drug content (as an example see figure 1).

In the following experiments (examples 1-3) a series of drug-carrier mixtures has been subjected to the amorphisation process according to the present invention.

Example 1

Physically homogeneous mixtures of Ibuprofen with β-cyclodextrine hydrate and Ibuprofen with Crosspovidone in weight ratios of 1 to 9 have been prepared; approx. 5 grams of the mixture, for each test, have been inserted into a Pyrex glass reactor (a material non-coupling with the microwaves) inside the applicator of the monomode oven. To each mixture, appropriately kept stirring by a mechanical stirrer in Pyrex glass (operating at 3 revolutions per minute), has been added an amount of purified water equal to 1 ml per gram of β–cyclodextrine and 2 ml per gram of Crosspovidone. The wet mixtures have then been subjected to treatment with microwaves at programmed temperature and at atmospheric pressure under the operative conditions reported in tables 1 and 2.

For Irradiation, a monomode "Synthewave 402" applicator from Prolabo has been used, operating at a frequency of 2.45 GHz and with a maximum deliverable power of 300 Watts.

The results obtained are illustrated in the two following tables.

*Table 1: operative conditions of the process and values of residual crystallinity of the Ibuprofen β–cyclodextrine composites obtained with the monomode applicator.*

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (*) (%) |
|---|---|---|---|---|
| Beta/Ibu13 | 10 | From 25 °C to 90 °C in 15' & 10' at 90 °C | 25 | 22.7 |
| Beta/Ibu14 | 10 | From 25 °C to 90 °C in 15' & 20' at 90 °C | 35 | 21.6 |

(*) % of crystallinity with respect to the crystallinity of the original drug (=100%).

*Table 2: operative conditions of the process and residual crystallinity values of the Ibuprofen Crosspovidone composites obtained with the monomode applicator.*

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| PVP/Ibu01 | 10 | From 25 °C to 90 °C in 15' & 10' at 90 °C | 25 | 0.0 |
| PVP/Ibu02 | 10 | From 25 °C to 80 °C in 15' & 15' at 90 °C | 30 | 0.0 |

The same approach has been used with a drug having different thermal characteristics to the previous (Nimesulide, $T_m$= 148.9 °C, $\Delta H_m$= 111.1 J/g). The method variations and the crystallinity data are reported in tables 3 and 4.

*Table 3: operative conditions of the process and residual crystallinity values of the Nimesulide β–cyclodextrine composites obtained with a monomode applicator.*

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| Beta/Nim01 | 10 | From 25 °C to 160 °C in 20' & 10' at 160 °C | 30 | 32.0 |
| Beta/Nim03 | 10 | From 25 °C to 160 °C in 20' & 20' at 160 °C | 40 | 40.7 |

*Table 4: operative conditions of the process and residual crystallinity values of the Nimesulide Crosspovidone composites obtained with a monomode applicator.*

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| PVP/Nim01 | 10 | From 25 °C to 150 °C in 20' & 10' a 150 °C | 30 | 45.4 |
| PVP/Nim02 | 10 | From 25 °C to 150 °C in 20' & 10' a 150 °C | 30 | 39.4 |
| PVP/Nim03 | 16.7 | From 25 °C to 100 °C in 15' & 15' a 100 °C | 30 | 38.0 |
| PVP/Nim04 | 16.7 | From 25 °C to 100 °C in 15' & 30' a 100 °C | 45 | 36.6 |

The same process has been used with Nifedipine, using the "Microsynth" multimode applicator. The process parameters and the crystallinity characteristics are reported in table 5.

*Table 5: operative conditions of the process and residual crystallinity values of the Nifedipine Crosspovidone composite obtained with the multimode applicator.*

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| PVP/Nif02 | 16.7 | From 25 °C to 175 °C in 15' & 10' at 175 °C | 35 | 0.0 |

The low or zero residual crystallinity percentages observed in the examples shown demonstrate

the achievement of high grades of amorphisation. In particular, in the case of ibuprofen and nifedipine, composites characterised by complete amorphisation of the drug (0% residual crystallinity) are obtained.

Regarding the degree of distribution of the drug within the carrier, the following data demonstrate that a massive dispersion (in-bulk) of the amorphised drug is achieved, i.e. not only on the surfaces of the carrier particles, but deep within them:

considering that the drug/polymer weight ratio used in the preceding experiments is equal to 1:5, (PVP-Vim 04) the mass balance of the composite is:

$$M_T = M_{DC} + M_{DA} + M_C$$

wherein: $M_{DC}$ represents the mass of the crystalline drug in the composite, $M_{DA}$ the mass of the amorphous drug, $M_C$ the mass of the carrier and $M_T$ the total mass.

For the examples reported, it will be:

$M_{DC} = 206.4mg * 0.366 = 75.5$,

$M_{DA} = 206.4mg - 75.5mg = 130.9$,

$M_C = 1028.9mg$ e $M_T = 1235.4mg$.

Since the PVP-CL used has a specific surface area of 4.5 $m^2/g$ (values determined experimentally by adsorbance isotherms B.E.T.) the weight fraction contained in the composite has a total surface development equal to 4.5 * 0.833= 3.75 $m^2/g$.

Reasonably, the drug molecules which can be stabilised in amorphous form on the surfaces of carriers constitute a molecular monolayer interacting with the surfaces themselves.

The drug molecule can interact with the molecules of polyvinylpyrrolidone, which are present on the surfaces of the carrier, with interactions which are either hydrophobic or hydrophilic in nature (remembering the amphiphilic nature of the polymer used); estimating the molecular surface development of the nimesulide, characterised by these two interactions, one can calculate the area occupied by a single molecule interacting with the surface.

Using the three dimensional molecular structure of nimesulide, minimised with both molecular mechanical (MMFF force field) and semi-empirical (AM1) algorithms with the software "Spartan 02", the two molecular describers involved can be calculated (molecular surface area with hydrophobic characteristics and molecular surface area with hydrophilic characteristics). The measurement of these describers has been performed with the molecular prediction software "QikProp" and has given the following values:

hydrophobic molecular surface area = 0.9 $nm^2$

hydrophilic molecular surface area = 1.75 $nm^2$

Considering the two contributions, the surface covered by a single molecule of nimesulide is equal to 2.65 $nm^2$.

The quantity of molecules necessary to constitute an amorphous monolayer on the surface of the

carrier will be given by 3.75 $m^2 \cdot g^{-1}$ / $2.65 \cdot 10^{-18} m^2$ = 140.7 $\cdot 10^{16}$ molecules, i.e. 0.721 mg of nimesulide. Rewriting the equation to balance with these values for $M_{DA}$, one obtains a value of $M_{DC}$ = 205.7 mg equal to 99.6% of crystallinity.

Hence, one can conclude that the excess of amorphous drug involved in preparation PVPNIM04 is found dispersed to a large measure inside (in-bulk) the carrier particles.

Example 2

Homogeneous physical mixtures of Nimesulide with Crosspovidone and β–cyclodextrine have been prepared in weight ratios 1 to 2 and 1 to 5, physical mixtures of Nifedipine with Crosspovidone 1 to 5 (w/w); approx. 5 grams of the mixture, for each test, have been inserted into a PTFE container loaded with graphite and then placed inside the application chamber of a multimode "Microsynth" oven (Mileston). In addition, a 1 to 9 Ibuprofen β–cyclodextrine mixture has been prepared and treated in the same oven, setting the power of the oven to a fixed and constant value, for the time of treatment, equal to 600 Watts. Water has not been added and the reaction environment has been maintained at atmospheric pressure (1 atm).

The process conditions and the physical characteristics of the composites obtained are reported in table 6.

*Table 6: operative conditions of the process and residual crystallinity values of the Nimesulide β–cyclodextrine, Ibuprofen β–cyclodextrine, Nimesulide Crosspovidone and Nifedipine Crosspovidone composites obtained with the multimode applicator.*

| Samples | (w/w)[a] | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| PVP/Nim05 | 1 to 2 | From 25 °C to 150 °C in 10' & 20' at 150 °C | 30 | 27.3 |
| PVP/Nif04 | 1 to 5 | From 25 °C to 175 °C in 15' & 10' at 175 °C | 25 | 1.0 |
| Betalbu15 | 1 to 9 | - | 5 | 23.8 |
| Betalbu16 | 1 to 9 | - | 3 | 38.4 |

(a) = weight ratio between drug and carrier

The residual crystallinity values indicate also in this case a high degree of amorphisation of the drug. The distribution in-bulk of the drug has been confirmed with the above described methods.

Example 3

A mixture of Nimesulide/Crosspovidone in a weight ratio of 1 to 5 has been prepared; approx. 6 grams of mixture have been inserted into the reactor of the multimode applicator. To the mixture have been added approx. 10 ml of purified water. The mixture, thus wetted, has been subjected to treatment with microwaves at temperature program temperature and at increasing pressure according to the phase diagram of water (at constant volume): from 1 bar (at T=25 °C) up to 5 bar (at T=155 °C).

The process conditions and the residual crystallinity obtained are reported in the following table 7:

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| PVP/Nim07 | 16.7 | From 25 °C to 155 °C in 10' & 10' at 155 °C and P=5 bar | 25 | 45.0 |

Example 4 (reference)

To verify the criticality of the treatment used in the present invention, Nimesulide- Crosspovidone and Nifedipine-Crosspovidone physical mixtures have been prepared in the weight ratio 1 to 5, approx. 2 grams of mixture have been introduced into a general reactor (in Pyrex glass) inside a monomode applicator. Differently from that requested in the present invention, water has not been added, and the reactor used is not based on dielectric materials coupling with the microwaves. The mixtures thus obtained have been successively subjected to treatment with microwaves at temperature program temperature and at reduced pressure ($0.1 * 10^5$ Pa) under the operative conditions reported in the table 8.

*Table 8: operative conditions and residual crystallinity values of the Nifedipine Crosspovidone and Nimesulide Crosspovidone composites.*

| Samples | Drug content (%) | Temperature program | Total time (minutes) | Residual crystallinity (%) |
|---|---|---|---|---|
| PVP/Nim06 | 16.7 | From 25 °C to 150 °C in 10' & 15' at 150 °C | 25 | 96.0 |

| | | | | |
|---|---|---|---|---|
| PVP/Nif01 | 16.7 | From 25 °C to 150 °C in 10' & 15' at 150 °C | 25 | 97.5 |

As is clear from the data of the percentage residual crystallinity (96-97%), the treatment has not been able to obtain any amorphisation: the drug maintains its crystallinity substantially unaltered. These data demonstrate that, in the absence of the conditions characterising the process of the invention, in particular the wetting of the drug-carrier mixture, or the use of reactors in materials coupling with the microwaves, it is not possible to obtain any dispersion of amorphised drug. In figures 2 and 3 are shown the temperature profiles of the two reference samples during the treatment cycle: as is clear from the figures, both mixtures treated do not have significant temperature increases such as to induce solid-liquid transitions in the crystalline drugs, even using the maximum power of the applicator used; that further confirms the absence of amorphisation of drug under these experimental conditions.

CLAIMS

1) A composite containing an active ingredient dispersed in an organic carrier, characterised by the fact that the active ingredient is massively dispersed (in-bulk) within the composite, and is present in amorphous form in a quantity greater than or equal to 50 % by weight, with respect to the total of drug present in the composite.

2) The composite according to claim 1, in which the active ingredient and the carrier are present in weight ratios comprised of between 1:0.5 and 1:20.

3) The composite according to claim 2, in which the active ingredient and the carrier are present in weight ratios comprised of between 1:1 and 1:10.

4) The composite according to claims 1-3, in which the organic carrier is selected from an insoluble cross-linked polymer, a hydrosoluble complexing agent, or mixtures thereof.

5) The composite according to claim 4, in which the insoluble cross-linked polymer is selected from cross-linked polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose, cross-linked starch, cross-linked dextran, cross-linked polystyrene, cross-linked β-cyclodextrine.

6) The composite according to claim 4, in which the hydrosoluble complexing agent is selected from alpha-cyclodextrine, beta-cyclodextrine, gamma-cyclodextrine, derivatives thereof, maltodextrine, microcrystalline cellulose.

7) The composite according to claims 1-6, in which said organic carrier has a surface area comprised of between 0.05 $m^2/g$ and 20 $m^2/g$.

8) The composite according to claims 1-7, in which said active ingredient is an active ingredient sparingly soluble in water.

9) The composite according to claim 8, in which said active ingredient is selected from nimesulide, ibuprofen, nifedipine, grisofulvine, piroxicam, progesterone, lorazepam.

10) The composite as described in the claims 1-9, for use in therapy.

11) A pharmaceutical composition containing the composite described in claims 1-9, possibly associated with pharmaceutically acceptable excipients.

12) The pharmaceutical composition according to claim 11, formulated as a granulate, pill, mini-pill, capsule, micro-capsule.

13) A procedure for the preparation of the composite described in claims 1-9, comprising the following steps:

a) form a wet mixture of said drug and said organic carrier;

b) irradiate the mixture obtained in a), with microwaves, at a pressure equal to or greater than the atmospheric pressure.

14) The procedure according to claim 13, in which said wet mixture is formed by adding water to the carrier-active ingredient composite in a quantity comprised of between 0.1 ml/g and 5 ml/g with respect to the dry mixture of the composite.

15) The procedure according to the claims 13-14, in which the pressure at which the irradiation is carried out is comprised of between 1 and 20 bar.

16) The procedure according to the claims 13-15, in which the irradiation with microwaves is

carried out in an energy range comprised of between 100 W and 5000 W for an overall time comprised of between 5 and 120 minutes.

17) A procedure for the preparation of the composite described in the claims 1-9, comprising the following steps:

a) mixing together said drug and said organic carrier;

b) placing the mixture obtained in a. in a container constituted of a dielectric material having coupling capacity with the microwaves;

c) irradiate, with microwaves, the container containing said mixture.

18) The procedure according to claim 17, in which said dielectric material is constituted of polytetrafluoroethylene loaded with graphite.

19) The procedure according to the claims 17-18, in which the irradiation with microwaves is carried out in an energy range comprised of between 100 W and 5000 W, for an overall time comprised of between 5 and 120 minutes.

20) A composite obtainable through the process described in the claims 13-19.

Milan, date

f. EURAND INTERNATIONAL S.p.A.

The Representative

(signature)

Dr. Diego Pallini

of NOTARBARTOLO & GERVASI S.p.A.

## DECLARATION UNDER 37 CFR 1.68

I, Giovanna Luisa Sarolo, declare

That I reside at Via Podgora 6, Milan, Italy;

That I am familiar with the Italian and English languages;

That I am a Sworn Translator, appointed by the Court of Milan, Italy;

That I have prepared the attached translation of the Italian Patent Application No. **MI2002 A 002748** filed on **23 December 2002** with the title: "Stabilized solid drug dispersions in an organic carrier and a procedure for preparing the same", said Italian language document being already filed at WIPO during the PCT procedure.

That the attached translation is complete and accurate and fairly reflects the meaning and content of said Italian language document.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Giovanna Luisa SAROLO

Milan, ITALY, 2nd December 2008